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# PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To: MELODIE W. HENDERSON
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# PCT

## COMMUNICATION IN CASES FOR WHICH NO OTHER FORM IS APPLICABLE

| | |
|---|---|
| | Date of Mailing *(day/month/year)* 01 APR 2003 |
| Applicant's or agent's file reference MWH-0002PCT | **REPLY DUE** See paragraph 1 below |
| International application No. PCT/US00/19094 | International filing date *(day/month/year)* 13 JULY 2000 |
| Applicant GENAISSANCE PHARMACEUTICALS, INC. | |

1. ☐ REPLY DUE within months~~/days~~ from the above date of mailing

☒ NO REPLY DUE

2. COMMUNICATION:

The International Preliminary Examination Report (form PCT/IPEA/409) mailed on 08 May 2001 is VACATED because it did not indicate that amended claim pages 74 - 78 filed with the demand formed the basis of the report. Attached is a Corrected IPER including an annex consisting of these amended sheets of claims.

| | |
|---|---|
| Name and mailing address of the IPEA/US<br>Commissioner of Patents and Trademarks<br>Box PCT<br>Washington, D.C. 20231 | Authorized officer<br>Carol Bidwell CB |
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Form PCT/IPEA/424 (January 1994)★

# PATENT COOPERATION TREATY

# PCT

corrected

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

| Applicant's or agent's file reference MWH-0002PCT | FOR FURTHER ACTION | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
|---|---|---|
| International application No. PCT/US00/19094 | International filing date *(day/month/year)* 18 JULY 2000 | Priority date *(day/month/year)* 18 JULY 1999 |
| International Patent Classification (IPC) or national classification and IPC Please See Supplemental Sheet. | | |
| Applicant GENAISSANCE PHARMACEUTICALS, INC. | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets.

☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 5 sheets.

3. This report contains indications relating to the following items:

- I [X] Basis of the report
- II [ ] Priority
- III [X] Non-establishment of report with regard to novelty, inventive step or industrial applicability
- IV [X] Lack of unity of invention
- V [X] Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI [ ] Certain documents cited
- VII [ ] Certain defects in the international application
- VIII [ ] Certain observations on the international application

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 13 FEBRUARY 2001 | 06 MARCH 2001 |
| Name and mailing address of the IPEA/US<br>Commissioner of Patents and Trademarks<br>Box PCT<br>Washington, D.C. 20231<br>Facsimile No. (703) 305-3230 | Authorized officer<br>Paige Bridgers for<br>PREMA MERTZ<br>Telephone No. (703) 308-0196 |

Form PCT/IPEA/409 (cover sheet) (July 1998)★

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US00/19094

## I. Basis of the report

1. With regard to the **elements** of the international application:*

☐ the international application as originally filed

☒ the description:
pages 1-73 , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

☒ the claims:
pages NONE , as originally filed
pages NONE , as amended (together with any statement) under Article 19
pages 74-78 , filed with the demand
pages NONE , filed with the letter of _____

☒ the drawings:
pages 1-15 , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

☒ the sequence listing part of the description:
pages 1-92 , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☒ contained in the international application in printed form.

☒ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the writen sequence listing has been furnished.

4. ☒ The amendments have resulted in the cancellation of:

☒ the description, pages NONE

☒ the claims, Nos. 2, 23

☒ the drawings, sheets/~~fig~~ NONE

5. ☐ This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

***Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US00/19094

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been and will not be examined in respect of:

☐ the entire international application.

☒ claims Nos. 11, 21-22 and 24-27

because:

☐ the said international application, or the said claim Nos. _ relate to the following subject matter which does not require international preliminary examination *(specify)*.

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _ are so unclear that no meaningful opinion could be formed *(specify)*.

☐ the claims, or said claims Nos. _ are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claims Nos. 11, 21-22 and 24-27 .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US00/19094

## IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:

Group I, claims 1, 3-10, 12, drawn to a polynucleotide encoding a polymorphic variant of IL4R alpha, a recombinant organism, the polymorphic variant of IL4R alpha and a method of screening for drugs targeting the polymorphic variant.

Group II, claim 11, drawn to an antibody to the variant.

Group III, claims 13-16, drawn to a composition comprising at least one genotyping oligonucleotide for detecting a polymorphism in a IL4R alpha gene.

Group IV, claim 17-20, drawn to a method of genotyping IL4R alpha.

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1, 3-10, 12-20.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US00/19094

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. statement

| | | | |
|---|---|---|---|
| Novelty (N) | Claims | 1, 3-10, 12-20 | YES |
| | Claims | NONE | NO |
| Inventive Step (IS) | Claims | 1, 3-10, 12-20 | YES |
| | Claims | NONE | NO |
| Industrial Applicability (IA) | Claims | 1, 3-10, 12-20 | YES |
| | Claims | NONE | NO |

2. citations and explanations (Rule 70.7)

Claims 1, 3-10, 12-20 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest an isolated polynucleotide as recited in claim 1, a recombinant organism transformed or transfected with the polynucleotide of claim 1, an isolated polynucleotide as recited in claim 7, a recombinant organism transformed or transfected with the polynucleotide of claim 7, an isolated polypeptide as recited in claim 10, a method for screening for drugs targeting the polypeptide of claim 10, a composition comprising at least one genotyping oligonucleotide as set forth in claim 18, and methods for genotyping or haplotyping the IL4Rα gene of an individual.

Claims 1, 3-10, 12-20 meet the criteria set out in PCT Article 33(4) for industrial utility.

---------- NEW CITATIONS ----------

NONE

**Supplemental Box**
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII



CLASSIFICATION:
The International Patent Classification (IPC) and/or the National classification are as listed below:
IPC(7): C12N 5/10, 15/12, 15/63, 15/64; C07K 14/47, 14/705, 14/715; GOIN 33/53, 33/567 and US Cl.: 530/350; 435/69.1, 71.1, 71.2, 325, 252.3, 254.11, 471, 6

What is Claimed is:

1. An isolated polynucleotide comprising a nucleotide sequence selected from the group consisting of:

(a) a first nucleotide sequence which is a polymorphic variant of a reference sequence for Interleukin 4 Receptor Alpha(IL4Rα) gene or a fragment thereof, wherein the reference sequence comprises SEQ ID NO:1, and the polymorphic variant comprises an IL4Rα isogene defined by a haplotype selected from the group consisting of haplotypes 1-53 in Table 5; and

(b) a second nucleotide sequence which is complementary to the first nucleotide sequence.

3. The isolated polynucleotide of claim 1 which is a DNA molecule and comprises both the first and second nucleotide sequences and further comprises expression regulatory elements operably linked to the first nucleotide sequence.

4. A recombinant organism transformed or transfected with the isolated polynucleotide of claim 1, wherein the organism expresses an IL4Rα protein encoded by the first nucleotide sequence.

5. The recombinant organism of claim 4 which is a nonhuman transgenic animal.

6. The isolated polynucleotide of claim 1, wherein the first nucleotide sequence is a polymorphic variant of a fragment of the IL4Rα isogene, the fragment comprising one or more polymorphisms selected from the group consisting of: guanine at PS1, thymine at PS2, thymine at PS3, cytosine at PS4, thymine at PS6, adenine at PS7, cytosine at PS8, thymine at PS9, thymine at PS10, adenine at PS11, adenine at PS12, thymine at PS13, thymine at PS14, adenine at PS15, thymine at PS16, adenine at PS17, thymine at PS18, adenine at PS19, cytosine at PS20, cytosine at PS21, thymine at PS22, cytosine at PS23, thymine at PS25, thymine at PS27, cytosine at PS28, thymine at PS30, adenine at PS32, thymine at PS33, guanine at PS34, cytosine at PS35, cytosine at PS36, cytosine at PS37, thymine at PS38, guanine at PS39, guanine at PS40, adenine at PS41, thymine at PS44, and adenine at PS45.

7. An isolated polynucleotide comprising a nucleotide sequence which is a polymorphic variant of a reference sequence for the IL4Rα cDNA or a fragment thereof, wherein the reference sequence comprises SEQ ID NO:2 and the polymorphic variant comprises adenine or guanine at a position corresponding to nucleotide 223, cytosine or thymine at a position corresponding to nucleotide 237, guanine or adenine at a position corresponding to

nucleotide 244, thymine or cytosine at a position corresponding to nucleotide 291, cytosine or thymine at a position corresponding to nucleotide 501, guanine or adenine at a position corresponding to nucleotide 554, thymine or cytosine at a position corresponding to nucleotide 939, adenine or cytosine at a position corresponding to nucleotide 1198, guanine or thymine at a position corresponding to nucleotide 1242, thymine or cytosine at a position corresponding to nucleotide 1291, cytosine or thymine at a position corresponding to nucleotide 1293, thymine or cytosine at a position corresponding to nucleotide 1299, thymine or cytosine at a position corresponding to nucleotide 1507, cytosine or thymine at a position corresponding to nucleotide 1701, adenine or guanine at a position corresponding to nucleotide 1727, guanine or adenine at a position corresponding to nucleotide 1735, cytosine or thymine at a position corresponding to nucleotide 2023, thynine or guanine at a position corresponding to nucleotide 2254 and thymine or cytosine at a position corresponding to nucleotide 2397.

8. A recombinant organism transformed or transfected with the isolated polynucleotide of claim 7, wherein the organism expresses a Interleukin 4 Receptor Alpha(IL4Rα) protein encoded by the polymorphic variant sequence.
9. The recombinant organism of claim 8 which is a nonhuman transgenic animal.
10. An isolated polypeptide comprising an amino acid sequence which is a polymorphic variant of a reference sequence for the IL4Rα protein or a fragment thereof, wherein the reference sequence comprises SEQ ID NO: 3 and the polymorphic variant is encoded by an isogene defined by one of the haplotypes shown in Table 5.
11. An isolated antibody specific for and immunoreactive with the isolated polypeptide of claim 10.
12. A method for screening for drugs targeting the isolated polypeptide of claim 10 which comprises contacting the IL4Rα polymorphic variant with a candidate agent and assaying for binding activity.
13. A composition comprising at least one genotyping oligonucleotide for detecting a polymorphism in the Interleukin 4 Receptor Alpha(IL4Rα) gene at a polymorphic site selected from PS1, PS2, PS3, PS4, PS6, PS7, PS8, PS9, PS10, PS11, PS12, PS13, PS14, PS15, PS16, PS17, PS18, PS19, PS20, PS21, PS22, PS23, PS25, PS27, PS28, PS30, PS32, PS33, PS34, PS35, PS36, PS37, PS38, PS39, PS40, PS41, PS44, and PS45.

14. The composition of claim 13, wherein the genotyping oligonucleotide is an allele-specific oligonucleotide that specifically hybridizes to an allele of the IL4Rα gene at a region containing the polymorphic site.
15. The composition of claim 14, wherein the allele-specific oligonucleotide comprises a nucleotide sequence selected from the group consisting of of SEQ ID NOS:4-79, the complements of SEQ ID NOS: 4-79, and SEQ ID NOS:80-231.
16. The composition of claim 13, wherein the genotyping oligonucleotide is a primer-extension oligonucleotide.
17. A method for genotyping the Interleukin 4 Receptor Alpha(IL4Rα) gene of an individual, comprising determining for the two copies of the IL4Rα gene present in the individual the identity of the nucleotide pair at each of PS1, PS2, PS3, PS4, PS6, PS7, PS8, PS9, PS10, PS11, PS12, PS13, PS14, PS15, PS16, PS17, PS18, PS19, PS20, PS21, PS22, PS23, PS25, PS27, PS28, PS30, PS32, PS33, PS34, PS35, PS36, PS37, PS38, PS39, PS40, PS41, PS44, and PS45.
18. The method of claim 17, wherein the determining step comprises:
    (a) isolating from the individual a nucleic acid mixture comprising both copies of the IL4Rα gene, or a fragment thereof, that are present in the individual;
    (b) amplifying from the nucleic acid mixture a target region containing at least one of the polymorphic sites;
    (c) hybridizing a primer extension oligonucleotide to one allele of the amplified target region;
    (d) performing a nucleic acid template-dependent, primer extension reaction on the hybridized genotyping oligonucleotide in the presence of at least two different terminators of the reaction, wherein said terminators are complementary to the alternative nucleotides present at the polymorphic site; and
    (e) detecting the presence and identity of the terminator in the extended genotyping oligonucleotide.
19. A method for haplotyping the Interleukin 4 Receptor Alpha(IL4Rα) gene of an individual which comprises determining, for one copy of the IL4Rα gene present in the individual, the identity of the nucleotide at each of PS1, PS2, PS3, PS4, PS6, PS7, PS8, PS9, PS10, PS11, PS12, PS13, PS14, PS15, PS16, PS17, PS18, PS19, PS20, PS21, PS22, PS23, PS25, PS27, PS28, PS30, PS32, PS33, PS34, PS35, PS36, PS37, PS38, PS39, PS40, PS41, PS44, and PS45.

20. The method of claim 19, wherein the determining step comprises
    (a) isolating from the individual a nucleic acid molecule containing only one of the two copies of the IL4Rα gene, or a fragment thereof, that is present in the individual;
    (b) amplifying from the nucleic acid molecule a target region containing at least one of the polymorphic sites;
    (c) hybridizing a primer extension oligonucleotide to one allele of the amplified target region;
    (d) performing a nucleic acid template-dependent, primer extension reaction on the hybridized genotyping oligonucleotide in the presence of at least two different terminators of the reaction, wherein said terminators are complementary to the alternative nucleotides present at the polymorphic site; and
    (e) detecting the presence and identity of the terminator in the extended genotyping oligonucleotide.

21. A method for predicting a haplotype pair for the Interleukin 4 Receptor Alpha(IL4Rα) gene of an individual comprising:
    (a) identifying an IL4Rα genotype for the individual at each of PS1, PS2, PS3, PS4, PS6, PS7, PS8, PS9, PS10, PS11, PS12, PS13, PS14, PS15, PS16, PS17, PS18, PS19, PS20, PS21, PS22, PS23, PS25, PS27, PS28, PS30, PS32, PS33, PS34, PS35, PS36, PS37, PS38, PS39, PS40, PS41, PS44, and PS45;
    (b) enumerating all possible haplotype pairs which are consistent with the genotype;
    (c) accessing data containing the IL4Rα haplotype pairs determined in a reference population; and
    (d) assigning a haplotype pair to the individual that is consistent with the data.

22. A method for identifying an association between a trait and at least one haplotype of the Interleukin 4 Receptor Alpha gene which comprises comparing the frequency of the haplotype in a population exhibiting the trait with the frequency of the haplotype in a reference population, wherein the haplotype is selected from haplotype numbers 1-53 shown in Table 5, wherein a higher frequency of the haplotype in the trait population than in the reference population indicates the trait is associated with the haplotype.

24. The method of claim 22, wherein the trait is a clinical response to a drug targeting IL4Rα .

25. A computer system for storing and analyzing polymorphism data for the Interleukin 4 Receptor Alphagene, comprising:
    (a) a central processing unit (CPU);

(b) a communication interface;

(c) a display device;

(d) an input device; and

(e) a database containing the polymorphism data;

wherein the polymorphism data comprises the genotypes and haplotype pairs shown in Table 4 and the haplotypes shown in Table 5.

26. A genome anthology for the Interleukin 4 Receptor Alpha(IL4Rα) gene which comprises IL4Rα isogenes defined by haplotypes 1-53 shown in Table 5.

27. A method for haplotyping the Interleukin 4 Receptor Alpha (IL4Rα) gene of an individual which comprises determining whether the individual has one or more haplotypes in Table 5.